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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/803,426	03/09/2001	Bruce Mortensen	0300-0016	4832

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EXAMINER

TRAN, MY CHAU T

ART UNIT	PAPER NUMBER
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1641

DATE MAILED: 04/23/2002

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/803,426	Applicant(s) MORTENSEN ET AL.	
	Examiner My-Chau T. Tran	Art Unit 1641	

-- Th MAILING DATE of this communication appears on th cover sheet with the correspond nc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-44 is/are pending in the application.
- 4a) Of the above claim(s) 1-25 and 38-44 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 26-37 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 23 July 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on ____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). ____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) <u>10</u> . | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. Applicant's response filed January 25, 2002 in Paper No. 9 is acknowledged. Claim 26 is amended.
2. The information disclosure statement filed January 25, 2002 in Paper No. 10 has been received.
3. In Paper No. 9, applicant has confirmed the election of Group II, claims 26-37, with traverse. The traversal is on the ground(s) that Group I-IV should be rejoin for the following reasons. The search and examination would not be burdensome if Group I and III-IV, claims 1-25 and 38-44, are rejoin with Group II because of overlapping features of cyanine 5 and fluorescein. Applicant argues that the claimed composition (Group II) and the claimed compound (Group III, claims 38-43) are "*clearly intended to be use*" in a FRET-based assay (Group IV, claim 44) and in the method for detecting the proximity of two molecular segments (Group I, claims 1-25).

This is not found persuasive because although there are overlapping features among these inventions, Group I-IV, the search requirement is *not* co-extensive that a search for one invention would *not encompass* the limitations of the other inventions thus resulting in divergent of the search evaluations.

Group I is drawn to *a method for detecting the proximity of two molecular segments*. Group II is drawn to *a composition of a binding pair*. Group III is drawn to *a compound of two molecular segments*. Group IV is drawn to *an improvement of a FRET-based assay*. Groups II

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and III are distinct inventions, which require different functions and effects. The feature of a binding pair of Group II is not required by the claim of Group III. The feature of a first and second molecular segments of Group III is not required by the claim of Group II. The features of Group II and III show that these inventions are unrelated and are not disclosed as capable of use together. Groups I and IV are distinct inventions for they require different method steps. The method step of detecting the presence or absence of fluorescein of Group I does not require the dye pair of Group IV. The method steps "a-c" of Group I further limit the binding characteristics of fluorescein and cyanine 5. Since either of Group II or Group III can be use in the process of either Group I or Group IV, which is disclosed by applicant. Then these inventions are distinct because the product (Group II or III) as claimed can be used in a materially different process (Group I or IV). Therefore the restriction is proper and Groups I and III-IV are not rejoined with Group II.

The requirement is still deemed proper and is therefore made **FINAL**.

Withdrawn Rejections

4. The previous rejections under 35 USC 102(b) for claims 26-27 have been withdrawn in view of applicant's amendments. Maintained rejections are set forth below along with response to arguments.

Maintained Rejections

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

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A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claim 33 is rejected under 35 U.S.C. 102(b) is maintained as being anticipated by Bernard et al (*Analytical Biochem*, 255:101-107, 1998).

Bernard et al. anticipated the invention of claim 33 by disclosing a complementary oligonucleotide binding pair (pg. 101, right col. 2nd paragraph; pg. 102, left col., lines 1-2 and 4-8). A member of the binding pair is directly attached to fluorescein (a complementary fluorescein probe) and the other member of the binding pair is directly attached to cyanine 5 (a Cy5-labeled PCR strand) (pg. 102, left col., lines 4-8). The binding pair is associated so that the fluorescein and cyanine 5 are in fluorescence resonance energy transfer to each other (pg. 102, left col., lines 30-44).

Response to Arguments

7. Applicant's arguments filed January 25, 2002 have been fully considered but they are not found persuasive. The examiner's rationale is set forth below.

8. Although applicant has amended Claim 26 in order to exclude the binding pair to be a complementary oligonucleotides. But Claim 33, which depends on Claim 26, recited that the binding pair comprises a complementary oligonucleotides. Thus, Claim 33 is treated to recite a binding pair that is a complementary oligonucleotide and that the first member of the binding pair is directly or indirectly attached to fluorescein and the second member of the binding pair is directly or indirectly attached to cyanine 5. Further, the binding pair is associated so that the

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fluorescein and cyanine 5 are in fluorescence resonance energy transfer to each other. Therefore, the rejection under 35 USC 102(b) is maintained for Claim 33.

9. In response to applicant's argument that the presently claimed invention is not concerned with DNA quenching of fluorescence for which the linker of Lee taught in regard to the 35 USC 103(a) for claims 28 and 29. But that the presently claimed invention is directed to use the linker for the observation of the fluorescence resonance energy transfer from the acceptor fluorophore's fluorescent emission, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

10. Applicant contends that Bernard teaches that fluorescence energy transfer between cyanine 5 and fluorescein only under very specific and restricted experimental conditions. The examiner deems that this is not the case for the *preliminary* work of Bernard has demonstrated that fluorescence energy transfer between cyanine 5 and fluorescein does occur and suggest that some separation is more efficient than no separation, with gradual decrease in energy transfer efficiency as the separation increases (pg. 106, col. left, lines 50-54), which imply that distance would be a contributing factor in energy transfer between cyanine 5 and fluorescein. Bernard further suggests that other resonance energy transfer designs can be envisioned (pg. 106, col. left, lines 42-43).

11. Applicant alleges that the teaching of Chick and Dykens would not use fluorescein with cyanine 5, because these fluorophores *do not* have overlapping excited state energy levels (i.e. there is **no** overlap between the donor emission spectrum and the acceptor excitation spectrum). The examiner contend that this is a conflicting statement since it is disclosed by applicant on pg. 6, lines 23-24 of the response that “*there are numerous factors that control energy transfer efficiencies, such as distance, orientation factors, and the overlap integral between the donor emission and the acceptor excitation spectrum.*” Therefore, for energy transfer to occur there must be some overlap between the donor emission spectrum and the acceptor excitation spectrum.

New Rejections ---Necessitated by Amendment

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 30-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. A broad range or limitation together with a narrow range or limitation that falls within the broad range or limitation is considered indefinite, since it does not clearly set forth the metes and bounds of the independent claim (Claim 26). In the present instance, claims 30-33 recite the broad recitation of *the binding pair comprises an enzyme-enzyme substrate pair (Claim 30), an antibody-antigen pair (Claim 31), a biological receptor-ligand pair (Claim 32), and*

complementary oligonucleotides (Claim 33), and the amended claim 26 recites the *binding pairs are selected from the group consisting of antigen-antibody, biotin-avidin, etc.*, which is the narrower statement of the range/limitation. See under 35 U.S.C 112, fourth paragraph. "A claim in dependent form shall contain a reference to a claim previously set forth and then specify a **further limitation** of the subject matter claimed." See also MPEP, 608.01 (n), "Infringement Test" for dependent claims. The test for a proper dependent claim is whether the dependent claim includes every limitation of the parent claim. The test is not whether the claims differ in scope. A proper dependent claim shall not conceivably be infringed by anything which would not also infringe the basic claim.

Claim Rejections - 35 USC § 103

15. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

16. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

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17. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

18. Claims 26-27, 30-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al (*Analytical Biochem*, 255:101-107, 1998) in view of Chick et al. (US Patent 6,040,194).

Bernard discloses binding pair, which is a complementary oligonucleotide (pg. 101, right col. 2nd paragraph; pg. 102, left col., lines 1-2 and 4-8). A member of the binding pair is directly attached to fluorescein (a complementary fluorescein probe) and the other member of the binding pair is directly attached to cyanine 5 (a Cy5-labeled PCR strand) (pg. 102, left col., lines 4-8). The binding pair is associated so that the fluorescein and cyanine 5 are in fluorescence resonance energy transfer to each other (pg. 102, left col., lines 30-44).

The binding pair of Bernard differs from the claimed invention in failing to teach the binding pair to include antibody-antigen, receptor-ligand, or enzyme-substrate.

Chick discloses the binding pair can also be antibody-antigen, receptor-ligand, or enzyme-substrate (col. 5, lines 22-32; col. 9, lines 43-50). Further, the binding pair directly attached to the fluorescein and cyanine 5 and is associated so that fluorescence resonance energy

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transfer can be observed (col. 10, lines 19-41). Chick incorporated these different analytes (binding pair) because the binding ability of these different analytes can be detected in a wide range of physiological concentrations (col. 2, lines 21-25).

It would have been obvious to one of ordinary skill in the art at the time the invention was made for the composition of Bernard et al with different combinations of binding pair as taught by Chick et al because in a wide range of physiological concentrations the binding ability of these different analytes can also be detected.

19. Claims 28 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al (*Analytical Biochem*, 255:101-107, 1998) in view of Chick et al. (US Patent 6,040,194) as applied to claims 26-27 and 30-33 above, and further in view of Lee et al (*Analytical Biochemistry*, 227: 295-301, 1995).

The binding pair of Bernard and Chick are disclose above.

Both Bernard and Chick differs from the claimed invention in failing to teach an indirect attachment of the binding pair the fluorescein and cyanine 5.

Lee discloses that the fluorophore moieties are attached via a linker to a binding pair (pg. 295, abstract; pg. 297, right col., line 5-10). The flexibility of the extrinsic fluorophore probe when it is attached to a longer linker causes heterogeneity of distance (pg. 297, col. left, lines 54-56), which would provide a more efficient fluorescence energy transfer. Since distance is one of several factor contributing to the efficiency of energy transfer.

It would have been obvious to one of ordinary skill in the art at the time the invention was made for the binding pair in Bernard as modify by ^{Chick}Johnson to be indirectly attached via a

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linker as taught by Lee because the linker would cause a heterogeneity of distance to provide a more efficient fluorescence energy transfer.

20. Claims 34-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al (*Analytical Biochem*, 255:101-107, 1998) in view of Chick et al. (US Patent 6,040,194) as applied to claims 26-27 and 30-33 above, and further in view of Dykens et al. (US Patent 6,280,981 B1).

The binding pair of Bernard and Chick are disclose above.

Both Bernard and Chick differs from the claimed invention in failing explicitly to teach the proximity of the fluorescence resonance energy transfer.

Dyken teaches that the efficiency of the resonance energy transfer is dictated largely by the proximity of the donor and acceptor (col. 15, line 38-52) and that those familiar with the art will readily appreciate that donor-acceptor intermolecular distance is a cardinal determinative factor for the efficiency of the resonance energy transfer (col. 31, line 14-17). Dykens et al list the proximity distance in col. 31, line 1-9.

It would have been obvious to one having ordinary skill in the art at the time the invention was made for the binding pair in Bernard as modify by ^{Chick}Johnson to the proximity distance as taught by Dykens for the advantage of providing a more efficient determination the resonance energy transfer in different combination of binding pair. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 105 USPQ 233.

Conclusion

21. No claims are allowed.

22. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to My-Chau T. Tran whose telephone number is 703-305-6999. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long V. Le can be reached on 703-305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-872-9307 for After Final communications.

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Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.



mct
April 19, 2002



LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

04/17/02